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PATENT

GROUP 1800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

HUGHES BLAUDIN DE THE; AGNES
MARCHIO; PIERRE TIOLLAIS; ANNE
DEJEAN; NIGEL BRAND; MARTIN
PETKOVICH; ANDREE KRUST; AND
PIERRE CHAMBON

Serial No.: 07/649,342

Filed: February 1, 1991

For: A NOVEL STEROID/THYROID
HORMONE RECEPTOR-RELATED
GENE INAPPROPRIATELY
EXPRESSED IN HUMAN
HEPATOCELLULAR CARCINOMA

Group Art Unit: 1812

Examiner: J. Ulm

APPELLANTS' REPLY BRIEF

LAW OFFICES

FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005
1-202-408-4000

Kenneth J. Meyers
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER
1300 I Street, N.W.
Washington, D.C. 20005-3315

(202) 408-4000



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FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
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For: A NOVEL STEROID/THYROID)
HORMONE RECEPTOR-RELATED)
GENE INAPPROPRIATELY)
EXPRESSED IN HUMAN)
HEPATOCELLULAR CARCINOMA)

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

APPELLANTS' REPLY BRIEF

This is Appellants' reply to the new issues raised in the
Examiner's Answer (Paper No. 28).

Appellants' claims relating to a retinoic acid receptor have
been rejected as being unpatentable over the Petkovich et al.
reference, which describes RAR- α , and two other prior art
references that do not describe retinoic acid receptors of any
kind. Appellants' invention and the gene disclosed in Petkovich
et al. are two different members of the retinoic acid receptor
family and are so recognized in the art. It is Appellants'
position that the prior art does not suggest the numerous

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structural modifications needed to obtain Appellants' gene, namely, RAR- β . The Examiner did not respond to Appellants' assertions, and in fact, conceded them:

At no point have the pending claims been rejected on a position that an artisan would have found it obvious to alter the DNA described in the Petkovich et al. publication to arrive at the claimed DNA. . . .

Examiner's Answer at page 6, lines 20-23.

The degree of homology between Appellants' DNA sequence and the sequence of Petkovich et al. varies throughout the molecule. The numerous differences in structure are not without significance, because as Appellants explained in their Appeal Brief, Appellants' receptor RAR- β exhibits different properties and different functions when compared with Petkovich's receptor RAR- α . It is Appellants' position that their invention would not have been *prima facie* obvious for these reasons, but the Examiner disagreed.

What then is the Examiner's position? It is evident from the Examiner's Answer that he has framed the issue in an entirely different way than Appellants.

In a well-articulated explanation of his position, the Examiner stated that:

. . . the Petkovich et al. publication described an isolated DNA encoding hRAR which is structurally related to the protein encoded by the claimed DNA, disclosed the chromosomal location and partial nucleotide sequence of the human gene corresponding to the claimed DNA (encoding hORF a.k.a. RAR- β) and reasonably speculated that hORF probably encodes a retinoic acid or retinol receptor, based upon the available evidence which included the 100% amino acid sequence identity between the N-terminal halves of the C regions of the encoded products hRAR (RAR- α) and hORF (RAR- β). The Petkovich et al. reference differs from the instant invention because it did not disclose a DNA encoding the entire

hORF product described therein, and additional fragments thereof.

The Hauptmann et al. and Krust et al. publications have been relied upon to exemplify the skill of an artisan at the time of the instant invention. These references show that the isolation of a DNA encoding one protein by screening a suitable DNA library with a DNA encoding a structurally related protein was routine in the art at the time that the instant invention was made, as was the construction of expression vectors and transformed cells containing such vectors.

The isolation of a DNA encoding the hORF gene product described in the Petkovich et al. reference by screening a liver cDNA library with either the DNA encoding hRAR or a DNA encoding part of the hORF product by those methods exemplified here by the Hauptmann et al. and Krust et al. publications would have been obvious to an artisan of ordinary skill at the time of the instant invention.

Examiner's Answer at pages 5-6. The evidence relied upon by the Examiner is insufficient to support a finding of *prima facie* obviousness and the Examiner's reasoning is unsupported by the current case law.

**THE IN RE BELL CASE SUPPORTS APPELLANTS'
CONTENTION THAT THEIR INVENTION WOULD NOT HAVE
BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL
IN THE ART AT THE TIME THE INVENTION WAS MADE**

Rationale of the type employed by the Examiner in rejecting Appellants' claims was rejected by the Court in In re Bell, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). The result reached by the Court in the Bell case supports Appellants' contention that their invention would not have been obvious to a person of ordinary skill in the art at the time the invention was made.

The Bell case involved the patentability of a gene encoding a protein. Appellants were claiming the gene as it occurred in nature, i.e., the native DNA sequence. In the Bell case, the

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existence of the gene was known, the protein it encoded was known, the function and properties of the protein were known, and the amino acid sequence of the protein was even known. The genetic code was also known. Because of the redundancy in the genetic code, there were a number of DNA sequences, including the native DNA sequence, that could encode the protein. Nevertheless, it was possible to write down every nucleotide sequence that encoded the protein, including the native nucleotide sequence.

It was the Examiner's position in the Bell case that given the amino acid sequence of the protein, the genetic code, and known techniques for isolating genes, it would have been obvious to probe the DNA of cells that produced the protein to isolate the native DNA. Once isolated, there was no controversy that the DNA could be sequenced. The Federal Circuit rejected the Examiner's reasoning.

The prior art in the present case provided the person of ordinary skill in the art with much less to work with than the skilled artisan had to work with in the Bell case. In the present case, a fragment of DNA had been identified and it was shown that the fragment exhibited homology to a region of a retinoic acid receptor, namely, RAR- α of Petkovich et al. It was not known whether the fragment was part of a gene of any kind. It was not known whether the fragment of DNA had any function. Even if the fragment was part of a gene, the function of the gene was unknown. Furthermore, the protein encoded by the gene was unknown. If the DNA fragment was part of a gene that encoded a protein, the structure and function of the protein were unknown. Moreover,

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unlike the Bell case where there were a large number of sequences each of which was easily determined from the genetic code, here there is an undetermined number of receptors in nature.

In the Bell case the Examiner argued that the gene was known to exist and methods were available for isolating the gene.

Notwithstanding these circumstances, the Court stated

. . . the PTO emphasizes the similarities between the method by which Bell made the claimed sequences and the method taught by [the prior art]. The PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions and the issue is the obviousness of the claimed compositions, not of the method by which they are made. See *In re Thorpe*, 777 F.2d 695, 697 (227 U.S.P.Q. 964, 966) (Fed. Cir. 1985) (The patentability of a product does not depend on its method of production).

Id. at 532. Surely the same rationale must apply in a case such as Appellants' where the existence of the gene was not even known!

Appellants are not claiming a method. They are claiming a composition having an admittedly unpredictable structure and unexpected properties. In the Examiner's own words:

At no point have the pending claims been rejected on the position that an artisan would have found it obvious to alter the DNA described in the Petkovich et al. publication to arrive at the claimed DNA. . . .

Examiner's Answer at page 6, lines 20-23. When the reasoning of the Court in the In re Bell case is applied to the case on appeal, the inescapable conclusion is that the compositions claimed by Appellants would not have been obvious to a person of ordinary skill in the art at the time Appellants made their invention. While the Examiner argues that methods were available for isolating Appellants' gene, "the issue is the obviousness of the claimed compositions, not of the method by which they are made."

Accordingly, the rejection should be reversed because the prior art does not suggest Appellants' compositions.

**THE DNA CLAIMED BY APPELLANTS
WAS UNKNOWN PRIOR TO THEIR DISCOVERY**

After articulating the scope and content of the prior art, the Examiner lapsed into an overstatement of what the prior art taught a person of ordinary skill in the art. Specifically, in describing Appellants' invention, the Examiner stated that:

Appellants' allegations that the RAR- β gene was unknown prior to Appellants' discovery is incorrect because this gene was known as the hORF gene described in the Petkovich et al. publication prior to the instant invention. . . .

Examiner's Answer at page 7, lines 1-4. A fragment of DNA was known, but the gene claimed by Appellants was unknown.

In this respect, it is important to understand the chronology of events in the prior art. Petkovich et al. discovered RAR- α , and in their publication they compared their discovery to a fragment of DNA in the prior art. The fragment of DNA was in fact obtained by Petkovich et al. from a prior publication made by Appellants. Specifically, the fragment was initially described by DeJean et al. in "Hepatitis B virus DNA integration in a sequence homologous to v-erb-A and steroid receptor genes in a hepatocellular carcinoma", NATURE, 332:70-72 (July 3, 1986), a copy of which is attached hereto as Exhibit 7 (to continue the exhibit numbering from the Appeal Brief). Thus, while the Examiner relied on the Petkovich et al. reference, the teachings in Petkovich were in fact Appellants' own disclosure of the DNA fragment.

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It is beyond controversy that Petkovich et al. did not discover the fragment. Appellants discovered the fragment, and not even Appellants knew its identity. Specifically, in the DeJean et al. article it was stated that:

We can thus speculate that the corresponding homologous region of [the DNA fragment], truncated by the exon-intron boundary, is part of a cellular gene that shares a common functional domain with hGR, ER and v-erb-A gene products and which could exert a transcriptional regulatory function on specific genes.

Exhibit 7 at pages 71-72; emphasis added. Contrary to the Examiner's assertion, the gene now claimed by Appellants was unknown prior to Appellants' discovery. There was speculation by DeJean et al. that the DNA fragment they identified may be part of a gene and they further speculated that it could encode a product having transcriptional regulatory functions on specific genes. The fact that the DNA was part of a gene, that it encoded a protein, that the protein had a specific structure and function, and that it may exert an effect were unknown prior to Appellants' invention.

The Examiner's subsequent statement that "The Petkovich et al. publication effectively place [*sic*, placed] the claimed DNA in the hands of an artisan of ordinary skill prior to the instant invention" is simply incorrect. There is no evidence of record that the DNA fragment described by DeJean et al. was part of a gene. A product in the prior art that was unappreciated may not be patent defeating. In re Marshall, 198 U.S.P.Q. 344 (C.C.P.A. 1978).

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**AN UNWARRANTED EXTRAPOLATION OF THE
TEACHINGS OF PETKOVICH ET AL. LED TO
AN UNSUPPORTABLE CONCLUSION OF OBVIOUSNESS**

The Examiner stated that

. . . the Petkovich et al. publication . . . reasonably speculated that hORF probably encodes a retinoic acid or retinol receptor, based upon the available evidence which included the 100% amino acid sequence identity between the N-terminal halves of the C regions of the encoded products hRAR (RAR- α) and hORF (RAR- β).

Examiner's Answer at page 5, lines 6-10. The indecision and uncertainty of the Examiner's own words that Petkovich et al. "reasonably speculated" that Appellants' fragment "probably encodes" a retinoic acid or retinol receptor further belies the Examiner's conclusion that the gene now claimed by Appellants was known.

In any event, in deciding the issue of obviousness, one must look at the prior art presented from a vantage point in time prior to when the invention was made and through the eyes of a hypothetical person of ordinary skill in the art. In re Carroll, 202 U.S.P.Q. 571, 572 (C.C.P.A. 1979). In addition, the references as a whole must be evaluated so that their teachings are applied in the context of their significance to a technician at the time -- a technician without knowledge of Appellants' invention. Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

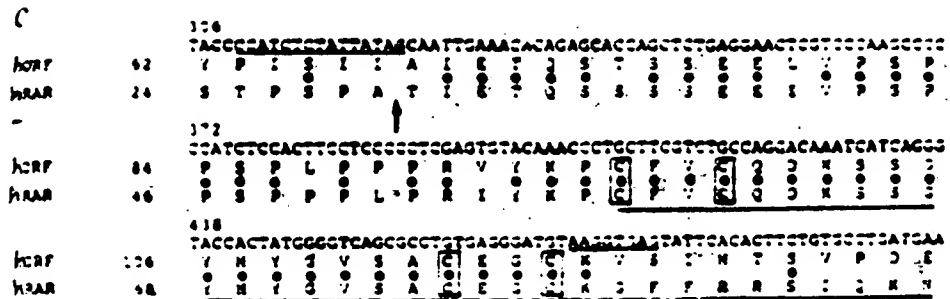
The only "available evidence" cited by the Examiner to support his assertion is the alleged "100% amino acid sequence identity" between the N-terminal halves of the C regions of RAR- α and RAR- β gene products. The allegation is incorrect. Petkovich

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et al. did not disclose 100% amino acid sequence identity in this region as will be evident from Figure 3(c) of the publication:



In this Figure, "hORF" identifies the DNA fragment previously described by DeJean et al. and "hRAR" identifies the RAR- α gene of Petkovich et al. The dots between the lines identify conserved amino acid residues between the two sequences. The Figure shows what a person of ordinary skill in the art would have seen "from a vantage point in time prior to when the invention was made", and it is evident that he would not have seen "100% amino acid sequence identity" as alleged by the Examiner.

Moreover, while the Examiner places great emphasis on the identity between certain amino acids and on homology in the C region of the DNA fragment in the prior art and Petkovich's RAR- α , the Examiner ignores Petkovich's specific observation that even the homology "ceases abruptly after amino acid 79". Petkovich et al. at page 448, col. 2, lines 8-13. It is well established that a prior art reference must be considered for all that it teaches and that it is improper to pick and choose from a

reference only those statements that support a rejection. See Akzo N.V. v. ITC, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986). It is improper to ignore the fact that no one knew what followed "amino acid 79". Furthermore, the prior art references must be read as a whole and consideration must be given where the references diverge from the claimed invention. Id. In view of the fact that homology "ceases abruptly after amino acid 79", the teachings of homology cease.

The RAR- β gene is 1344 nucleotides long. The Examiner's statement about homology in a short stretch of amino acids ignores the fact that it was discovered that there was only 64% amino acid sequence homology between RAR- α and RAR- β after Appellants' invention was made. See Brand et al., "Identification of a second human retinoic acid receptor", Nature, 322:850-853 (1988), at Fig. 1 (b) and (c). A copy of the Brand et al. publication is attached to Appellants' Brief On Appeal as Exhibit 5. It is this difference, and the consequences of this difference, that render Appellants' invention patentable.

Furthermore, even if one had "reasonably speculated" that Appellants' fragment was a "retinol receptor" as suggested by the Examiner, the speculation would have been wrong. Appellants' observed that the protein encoded by their gene did not bind with tritiated retinol. See de The et al., "A novel steroid thyroid hormone receptor-related gene inappropriately expressed in human hepatocellular carcinoma," Nature, 330:667-670 (1987), at page 668, col. 1, lines 4-8 of text. A copy is attached as Exhibit 8. Nevertheless, Appellants' gene was found to encode a receptor that

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does bind retinoic acid. See Brand et al., Exhibit 5, in the Abstract.

Like all legal conclusions, obviousness must rest on a foundation constructed of all the relevant and probative facts found in light of all the evidence. If that foundation crumbles, the legal conclusion on which it rests must fall. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983). The foundation for obviousness here is the Petkovich et al. publication and the comparison of a known DNA fragment with RAR- α newly discovered by Petkovich et al. The evidence on which the foundation is constructed includes "100% amino acid identity" and that Appellants' gene may be a "retinol receptor". As Appellants have shown, however, these facts are not substantiated by the evidence. There is not 100% amino acid identity in the C region, and in fact there is only 64% homology overall. In addition, Appellants' gene RAR- β does not encode a retinol receptor. The foundation has failed and the conclusion of obviousness is unsupportable.

**THE REJECTION OF APPELLANTS' CLAIMS
BASED ON WHAT WAS UNKNOWN MUST BE REVERSED**

Appellants separately argued the patentability of claims 4-9 and 57 directed to regions of DNA from the gene discovered by Appellants. The Examiner indicated that it would have been obvious to isolate these regions once the gene was known and that it was known that the gene was a member of a family of receptors having similar DNA domains. Examiner's Answer at pages 7-8. The Examiner made a similar argument with respect to claims 39, 41,

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& DUNNER
1300 I STREET, N. W.
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42, 46-52, 54-56, and 59, which were separately argued by Appellants. Examiner's Answer at page 8.

The fallacy in the reasoning is that only a fragment of DNA was known in the art and that it exhibited homology to a region of DNA of a retinoic acid receptor newly discovered by Petkovich et al. That the fragment was part of a gene was unknown as shown by the statement of DeJean et al., *supra*, who speculated that the fragment may be part of a gene that encoded a protein of unknown function. That the DNA fragment may have been part of a gene that encoded a receptor of any kind was also unknown. Obviousness cannot be predicated on what is unknown. In re Newell, 13 U.S.P.Q.2d 1248 (Fed. Cir. 1989). The rejection of all these claims must be reversed because there was no way of knowing that the claimed regions existed before Appellants discovered that the DNA fragment was part of a gene encoding a receptor that had domains similar to those of known receptors.

CONCLUSION

Appellants' invention would not have been *prima facie* obvious in view of the prior art because the prior art does not suggest the numerous structural modifications needed to obtain Appellants' gene. Appellants are claiming a composition, and the issue is the obviousness of the claimed composition, not the method by which it is made. In re Bell, *supra*. Appellants respectfully request that the rejection be reversed.

* * *

If there are any other fees due in connection with the filing of this Reply Brief, the Commissioner is authorized to charge any such fees to Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

Dated: January 24, 1994 By: Kenneth J. Meyers
Kenneth J. Meyers
Reg. No. 25,146

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& DUNNER

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